Risk of Hospitalized Gastrointestinal Bleeding in Persons Randomized to Diuretic, ACE-Inhibitor, or Calcium-Channel Blocker in ALLHAT

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Calcium channel blockers (CCBs) are an important class of medication useful in the treatment of hypertension. Several observational studies have suggested an association between CCB therapy and gastrointestinal (GI) hemorrhage. Using administrative databases, the authors re-examined in a post-hoc analysis whether the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) participants randomized to the CCB amlodipine had a greater risk of hospitalized GI bleeding (a prespecified outcome) compared with those randomized to the diuretic chlorthalidone or the angiotensin-converting enzyme inhibitor lisinopril. Participants randomized to chlorthalidone did not have a reduced risk for GI bleeding hospitalizations compared with participants randomized to amlodipine (hazard ratio [HR], 1.09; 95% confidence interval [CI], 0.92–1.28). Those randomized to lisinopril were at increased risk of GI bleeding compared with those randomized to chlorthalidone (HR, 1.16; 95% CI, 1.00–1.36). In a post-hoc comparison, participants assigned to lisinopril therapy had a higher risk of hospitalized GI hemorrhage (HR, 1.27; 95% CI, 1.06–1.51) vs those assigned to amlodipine. In-study use of atenolol prior to first GI hemorrhage was related to a lower incidence of GI bleeding (HR, 0.69; 95% CI, 0.57–0.83). Hypertensive patients on amlodipine do not have an increased risk of GI bleeding hospitalizations compared with those taking either chlorthalidone or lisinopril. *J Clin Hypertens (Greenwich).* 2013;15:825–832. ©2013 Wiley Periodicals, Inc.

Calcium channel blockers (CCBs) are a commonly prescribed class of antihypertensive medications.[1] Numerous studies have demonstrated the efficacy of CCBs in controlling blood pressure (BP) and preventing the adverse effects of chronic hypertension, except for heart failure.[2–9] In the previous 2 decades, several investigators have raised concern about possible prohemorrhagic activity of CCBs, citing an association between use of CCBs and the occurrence of cerebral,[10] surgical,[11] or gastrointestinal (GI) hemorrhage.[12–17] Laboratory studies have also suggested that both dihydropyridine and nondihydropyridine CCBs impair platelet activity, providing a possible mechanistic basis for the putative prohemorrhagic activity of CCBs.[18–21]

Nevertheless, the evidence regarding risk of bleeding associated with CCBs is inadequate for several reasons. First, there is a lack of randomized clinical trial evidence supporting the association between CCBs and GI hemorrhage, relative to other classes of antihypertensive agents. Second, there has been a failure to account for the differences between the 2 classes (dihydropyridine vs nondihydropyridine) of CCBs or specific agents.

Because uncontrolled hypertension is a prevalent and significant risk factor for cardiovascular disease, appropriate treatment of hypertension with proven safe medications is a critically important aspect of efforts to improve public health. Adequately powered, randomized clinical trials provide the best available evidence for determining the efficacy and safety of therapeutic agents. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[8] is the largest single randomized clinical trial undertaken to compare the relative efficacy of antihypertensive therapy in preventing hypertension-related complications. The trial, which compared lisinopril-, amlodipine-, and doxazosin-based regimens to a chlorthalidone-based reference population, has provided significant data regarding the safety and efficacy of these specific drugs, representing 4 classes of antihypertensive agents. ALLHAT previously reported the risk of hospitalization with GI hemorrhage for the prespecified comparisons of amlodipine[8] (hazard ratio [HR], 0.92; 95% confidence interval [CI], 0.82–1.03) or lisinopril[8] (HR, 1.11; 95% CI, 0.99–1.24) with chlorthalidone, and for a post-hoc comparison of lisinopril with amlodipine[22] (HR, 1.20; 95% CI, 1.06–1.37).

The purpose of this report is to re-examine these results utilizing a cohort defined by a revised set of

*A list of the ALLHAT Collaborative Research Group members has been published previously, in *JAMA*. 2002;288:2981–2997.

Clinical Trial Registration: www.clinicaltrials.gov/, NCT00000542.

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International Classification of Diseases (*ICD*) codes for GI bleeding hospitalizations and to explore in detail the issue regarding the association between selected classes of antihypertensive therapy and hospitalizations with GI hemorrhage.

METHODS

The rationale and design of ALLHAT have been described previously.[23–25] Briefly, eligible participants for ALLHAT were men and women 55 years or older who had systolic BP (SBP) of at least 140 mm Hg and/or diastolic BP (DBP) of at least 90 mm Hg or took medication for hypertension and had at least 1 additional risk factor for coronary heart disease (CHD). These risk factors included previous myocardial infarction (MI) or stroke (>6 months or age indeterminate), other atherosclerotic cardiovascular disease (ASCVD), ischemic changes on electrocardiography within the past 2 years, left ventricular hypertrophy (LVH) by electrocardiography or echocardiography, type 2 diabetes, current cigarette smoking, and low levels of high-density lipoprotein (HDL) cholesterol (<35 mg/dL). Details of the inclusion and exclusion criteria have been described previously.[24,25] Eligible participants were randomized into the trial at visit 2, at which time all prior antihypertensive medications were discontinued. From February 1994 to January 1998, 42,418 participants were recruited in 623 centers in the United States, Canada, Puerto Rico, and the US Virgin Islands.[25,26] All participants signed an informed consent form, and all centers received institutional review board approval.

Participants were assigned by a computer-generated randomization schedule to 1 of 4 treatments: chlorthalidone, amlodipine, lisinopril, or doxazosin, in a ratio of 1.7:1:1:1, respectively. Randomization was stratified by center and blocked over time to maintain the ratio. More participants were assigned to chlorthalidone in accordance with Dunnett's[27] multiple comparison procedure for comparing 3 treatment groups to a single control group. The treatment goal in each study arm was a BP <140/90 mm Hg. Because the doxazosin study arm was terminated early, resulting in differential follow-up time, we have not included data from the doxazosin arm of ALLHAT.

All study drugs were identical in appearance and masked at each of 3 dosage levels: 12.5 mg/d, 12.5 mg/d (sham titration), and 25 mg/d for chlorthalidone; 2.5 mg/d, 5 mg/d, and 10 mg/d for amlodipine; and 10 mg/d, 20 mg/d, and 40 mg/d for lisinopril. If participants did not meet the BP goal at the maximum tolerated dosage for the initial medication, an open-label step 2 agent (but not a medication from the same class as any of the study drugs) was titrated in 3 doses until goal was reached. The step 2 agents were atenolol (25–100 mg/d), reserpine (0.05–0.2 mg/d), and clonidine (0.1–0.3 mg twice per day). If goal BP was still not achieved, an open-label step 3 agent, hydralazine (25–100 mg twice per day), could be added. After initial titration visits, participants were seen routinely every 3 months during the first year and every 4 months thereafter for an average of 4.9 years (range: 3 years, 8 months to 8 years, 1 month) of follow-up.

Nonstudy open-label drugs could also be added to or substituted for step 2 or step 3 open-label medications to improve tolerance or BP control. However, use of open-label medications from one of the masked classes of drugs was to be avoided unless a compelling indication, such as heart failure, arose for one of the masked classes of drugs. A medication dose could be decreased or a medication stopped if it was believed to be causing adverse effects.

Data regarding aspirin use were collected through patient self-report at baseline and every 2 years throughout the active study. Information regarding the use of nonsteroidal anti-inflammatory drugs (NSAIDs), anticoagulants and other antiplatelet agents, and alcohol use was not collected.

The occurrence of hospitalizations with GI bleeding (a prespecified secondary outcome[23,28]) was not directly collected by ALLHAT clinics. Data regarding hospitalized GI bleeding (yes or no) were obtained through passive surveillance of participants treated as Medicare beneficiaries or within the Veterans Affairs (VA) health system for 1994 to 2001. Our initial cohort included 24,783 individuals who entered the Medicare system between 1994 and 2001 or were still in the VA system at the close of ALLHAT. Our new cohort consists of 20,844 individuals who were eligible for Medicare or in the VA systems at their entry into ALLHAT. As such, our new analysis includes 62% of participants randomized to the chlorthalidone-, lisinopril-, or amlodipine-based treatment arms in ALLHAT. Events were identified through CMS and VA data using relevant *ICD-Ninth Revision* (*ICD-9*) codes. In this analysis, GI bleeding was identified if the hospital records had one of the following *ICD-9* codes as either a primary or secondary diagnosis code: 531.0/2/4/6, 532.0/2/4/6, 533.0/2/4/6, 534.0/2/4/6, 535.01/11/21/31/41/51/61, and 578.x.[29] The previous definition used in ALLHAT also used codes 459.0, 997.02, 998.1, 998.11, 998.12, 99.03, 99.04, and 99.05, which captured unspecified and procedural hemorrhages and transfusions.[8]

Statistical Methods

Baseline characteristics were compared for participants with and without hospitalized GI bleeding using Student's *t* test for continuous variables and contingency table analyses for categorical data, overall and by treatment group. Hospitalized GI bleeding data were analyzed according to participants' randomized treatment assignments regardless of their subsequent medication status (ie, intention-to-treat analysis). Cumulative event rates were calculated using the Kaplan-Meier procedure. Cox proportional hazards models were used to obtain HRs and 95% CIs for the time to the first hospitalized GI bleed, adjusting for both baseline and time-dependent covariates. No corrections are made for multiple comparisons.

RESULTS

Table I presents the baseline characteristics of the study population by occurrence of hospitalization with GI bleeding. During a mean of 4.9 years of active follow-up, we identified 915 participants who were hospitalized with GI bleeding as the primary or secondary diagnosis. Participants who developed hospitalized GI bleeding were older, more likely to be male and non-Hispanic, and had lower educational attainment. Compared with those without GI bleeding hospitalization, they were similarly likely to be taking aspirin at baseline (40.5% vs 39.4%) and more likely to have diabetes, a history of MI or stroke, a history of ASCVD, and/or LVH on baseline electrocardiography. They were less likely to be taking estrogen (among women) and/or to be enrolled in the ALLHAT Lipid-Lowering Trial (ALLHAT-LLT), likely because of the ALLHAT-LLT eligibility criteria. Aspirin use at baseline was not different between participants randomized to any of the treatment groups (data not shown). Sixty percent of participants who were not diabetic at baseline also took aspirin, compared with 40% of diabetic participants (data not shown).

TABLE I. Baseline Characteristics by Occurrence of Hospitalized GI Bleeding

	Participants, No. (%)		
	GI Bleed	No GI Bleed	*P* Value
Participants randomized, No.[a]	915	19,929	
Age, mean (SD), y	72.0 (7.1)	70.3 (6.8)	<.001
55–64	119 (13.0)	3210 (16.1)	.012
65+	796 (87.0)	16,719 (83.9)	
Sex			
Women	340 (37.2)	8375 (42.0)	.004
Men	575 (62.8)	11,554 (58.0)	
Black/non-black			
Black	340 (37.2)	6800 (34.1)	.06
Non-black	575 (62.8)	13,129 (65.9)	
Hispanic/non-Hispanic			
Hispanic	119 (13.1)	3278 (16.5)	.007
Non-Hispanic	787 (86.9)	16,561 (83.5)	
Education, mean (SD), y	10.3 (4.0)	10.8 (4.1)	.001
Antihypertensive treatment			
Treated	849 (92.8)	18,208 (91.4)	.13
Untreated	66 (7.2)	1720 (8.6)	
Aspirin use at baseline	371 (40.5)	7853 (39.4)	.72
Women taking estrogen	33 (10.0)	1190 (14.5)	.03
HDL, mean (SD), mg/dL	46.3 (15.5)	46.6 (14.7)	.58
HDL <35 mg/dL	103 (11.3)	2470 (12.4)	.31
Diabetes classification[a]			
Diabetes	409 (48.3)	7845 (42.4)	.001
Nondiabetes	437 (51.7)	10,666 (57.6)	
Body mass index, mean (SD), mg/kg^2	28.8 (6.0)	29.1 (5.8)	.13
Cigarette smoker (yes/no)	186 (20.3)	3713 (18.6)	.20
History of CHD	281 (31.3)	5699 (28.8)	.12
Atherosclerotic CVD	558 (60.1)	11,234 (56.8)	.006
History MI or stroke	309 (33.8)	5289 (26.5)	<.001
History coronary revascularization	143 (15.6)	2985 (15.0)	.59
Other atherosclerotic CVD	275 (30.1)	5124 (25.7)	.003
ST-T wave	88 (9.8)	2080 (10.6)	.48
LVH by Minnesota code	65 (8.2)	913 (5.3)	<.001
Lipid trial participants	184 (20.1)	4688 (23.6)	.02

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; GI, gastrointestinal; HDL, high-density lipoprotein; LVH, left ventricular hypertrophy; MI, myocardial infarction; SD, standard deviation.

[a]History of diabetes at baseline or fasting glucose ≥126 mg/dL.

The Figure shows the cumulative hospitalized GI bleeding rates by randomized treatment group, and Cox regression analysis (Table II) revealed no significant difference between the chlorthalidone and amlodipine treatment groups (HR, 1.09; 95% CI, 0.92–1.28). However, when compared with amlodipine- or chlorthalidone-, the lisinopril-treated participants had a significantly higher risk of hospitalized GI bleeding (HR, 1.27; 95% CI, 1.06–1.51 and HR, 1.16; 95% CI, 1.00–1.36, respectively). There were no significant differences in treatment effect (ie, interactions) when analyzed by race, sex, ethnicity, aspirin use, or smoking at baseline. When limiting the sample to participants taking monotherapy, the findings were similar for the amlodipine vs chlorthalidone (HR, 1.05; 95% CI, 0.80–1.39) comparison. The HRs for the monotherapy cohort were higher, however, for the lisinopril vs amlodipine comparisons (HR, 1.52; 95% CI, 1.12–2.07) and for the lisinopril vs chlorthalidone comparisons (HR, 1.44, 95% CI, 1.12–1.87) (data not shown). Table III provides the cumulative incidence of participants, by treatment arm, with a hospitalized GI bleed by the end of years 1, 3, and 5. Of the 3 treatment arms, participants assigned to the amlodipine group experienced the lowest

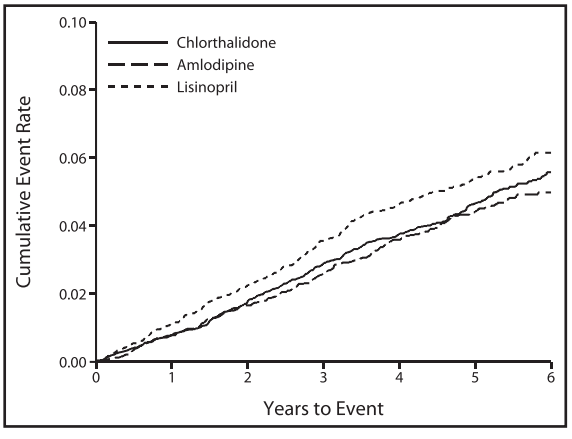

FIGURE. Hospitalizations with gastrointestinal bleed by treatment group.

TABLE II. Cox Regressions for Hospitalized GI Bleeding

				Unadjusted HR (95% CI)[a]		
	Amlodipine	Chlorthalidone	Lisinopril	Chlorthalidone vs Amlodipine	Lisinopril vs Amlodipine[b]	Lisinopril vs Chlorthalidone
Total	226/5674	410/9534	279/5631	1.09 (0.92–1.28)	1.27 (1.06–1.51)	1.16 (1.00–1.36)
Black	89/1917	146/3216	105/1928	0.98 (0.75–1.28)	1.19 (0.90–1.58)	1.22 (0.95–1.56)
Non-black	137/3713	264/6228	174/3642	1.15 (0.94–1.42)	1.31 (1.05–1.64)	1.13 (0.94–1.37)
P value for interaction				.34	.61	.66
Male	140/3281	255/5472	180/3287	1.10 (0.89–1.35)	1.30 (1.04–1.62)	1.19 (0.98–1.43)
Female	86/2349	155/3972	99/2283	1.07 (0.82–1.40)	1.20 (0.90–1.61)	1.12 (0.87–1.45)
P value for interaction				.90	.70	.75
Hispanic	26/738	48/1237	30/755	1.10 (0.69–1.78)	1.13 (0.67–1.92)	1.03 (0.65–1.62)
Non-Hispanic	200/4892	362/8207	249/4815	1.08 (0.91–1.29)	1.28 (1.06–1.55)	1.18 (1.01–1.39)
P value for interaction				.94	.67	.58
Aspirin at baseline	92/2253	159/3712	120/2227	1.07 (0.82–1.38)	1.35 (1.03–1.77)	1.27 (1.00–1.61)
No aspirin at baseline	133/3323	247/5633	156/3285	1.09 (0.88–1.35)	1.19 (0.95–1.50)	1.09 (0.89–1.33)
P value for interaction				.68	.50	.34
Age 55–64 y	27/914	57/1517	35/863	1.30 (0.82–2.06)	1.39 (0.84–2.30)	1.07 (0.70–1.63)
Age 65+ y	199/4716	353/7927	244/4707	1.06 (0.89–1.26)	1.24 (1.03–1.50)	1.18 (1.00–1.39)
P value for interaction				.41	.69	.68
Nonsmoker	188/4577	323/7672	218/4545	1.03 (0.86–1.23)	1.18 (0.97–1.44)	1.15 (0.97–1.36)
Smoker	38/1052	87/1772	61/1025	1.36 (0.93–1.99)	1.68 (1.12–2.52)	1.24 (0.89–1.71)
P value for interaction				.20	.13	.70

Abbreviations: CI, confidence interval; GI, gastrointestinal.

[a]Total hazard ratios (HRs) adjusted for race, sex, ethnicity, aspirin use at baseline, age, and smoking (not shown) are similar.

[b]Post-hoc comparison.

bleeding incidence over the entire trial, although it was statistically indistinguishable from the chlorthalidone group.

Table IV provides data on comparative effects of antihypertensive therapy on the occurrence of hospitalizations with GI bleeding after adjusting for selected baseline characteristics and subsequent (in-trial) use of aspirin and atenolol. The adjustment essentially yielded similar results to those in Table II. Baseline aspirin and atenolol use had no significant effect on hospitalized GI bleeding risk; however, in-trial atenolol use significantly reduced the risk for hospitalized GI bleeding (HR, 0.69; 95% CI, 0.57–0.83) whereas in-trial aspirin use did not affect subsequent risk. Age, current smoking, and male sex were also significant risk factors for hospitalized GI bleeding.

DISCUSSION

During the previous 2 decades, several investigators have presented data associating calcium channel antagonists with GI hemorrhage,[12] "life-threatening bleeding,"[30] increased perioperative blood transfusion requirements,[16] and declining hemoglobin concentrations among hospitalized patients.[15]

This report demonstrates that participants randomized to the amlodipine-based antihypertensive regimen have a similar occurrence of hospitalizations with GI bleeding to that of participants randomized to the chlorthalidone-based therapy. When the lisinopril and amlodipine treatment arms were compared in a post-hoc comparison, participants randomized to the amlodipine regimen had a significantly lower occurrence of GI bleeding hospitalizations. In a protocol-specified comparison of lisinopril vs chlorthalidone treatment groups, participants in the chlorthalidone arm had a marginally lower risk of hospitalized GI bleed (HR, 1.16; 95% CI, 1.00–1.36), similar to that previously reported (HR, 1.11; 95% CI, 0.99–1.24).[8] The population in this manuscript consists of the 915 participants who were hospitalized for GI bleeding during ALLHAT. These participants were drawn from the 20,844 who were on Medicare or in the VA system from time of randomization and throughout the study. The previous analyses[8] were based on the 24,783 ALLHAT participants who entered Medicare at some time during the study or were still in the VA system at the end of ALLHAT. The smaller cohort in this study ensures a more consistent and complete follow-up time for all of the participants, thus allowing us to present a more in-depth analysis than that which was published previously.

These new analyses, which used a more stringent definition and more restricted cohort, were quite similar to those initially reported. Subgroup analyses by race, sex, ethnicity, and baseline aspirin use also did not identify any differences in risk for hospitalized GI bleeding between the chlorthalidone- and amlodipine-based treatment arms.

TABLE III. Cumulative Proportion of Participants With Hospitalized GI Bleeding by Year and Treatment Group by Race, Sex, Ethnicity, Age, and Smoking

	Cumulative Incidence of Hospitalized GI Bleed per 1000 Participants (95% CI) at the End of the Specified Year		
Treatment Group	Year 1	Year 3	Year 5
Total			
Chlorthalidone	7.9 (6.2–9.9)	28.9 (25.6–32.6)	46.6 (42.1–51.5)
Amlodipine	7.9 (5.8–10.6)	26.0 (22.0–30.7)	44.4 (38.9–50.7)
Lisinopril	11.1 (8.6–14.3)	35.6 (30.9–41.0)	54.0 (47.9–60.9)
Non-black			
Chlorthalidone	8.1 (6.1–10.7)	28.7 (24.7–33.3)	45.1 (39.8–51.2)
Amlodipine	9.1 (6.5–12.8)	23.8 (19.3–29.5)	40.6 (34.2–48.2)
Lisinopril	10.7 (7.8–14.7)	34.1 (28.5–40.8)	51.8 (44.5–60.2)
Black			
Chlorthalidone	7.4 (4.9–11.1)	29.3 (23.8–36.1)	49.4 (41.8–58.4)
Amlodipine	5.4 (2.9–10.0)	30.2 (23.2–39.4)	51.9 (42.1–64.0)
Lisinopril	11.9 (7.8–18.0)	38.4 (30.4–48.5)	58.3 (48.0–70.9)
Women			
Chlorthalidone	8.3 (5.9–11.7)	28.0 (23.1–33.9)	42.5 (36.1–49.9)
Amlodipine	9.6 (6.3–14.6)	25.3 (19.5–32.7)	41.6 (33.5–51.5)
Lisinopril	10.9 (7.3–16.2)	29.8 (23.3–38.0)	50.0 (40.8–61.1)
Men			
Chlorthalidone	7.5 (5.5–10.2)	29.6 (25.3–34.6)	49.5 (43.5–56.3)
Amlodipine	6.6 (4.3–10.1)	26.5 (21.3–32.9)	46.6 (39.3–55.1)
Lisinopril	11.2 (8.1–15.5)	39.6 (33.3–47.2)	56.9 (49.0–66.1)
Non-Hispanic			
Chlorthalidone	8.4 (6.6–10.6)	28.4 (24.9–32.4)	46.4 (41.7–51.6)
Amlodipine	7.6 (5.5–10.5)	25.7 (21.4–30.7)	44.5 (38.6–51.2)
Lisinopril	11.5 (8.8–15.0)	36.6 (31.5–42.6)	54.9 (48.3–62.3)
Hispanic			
Chlorthalidone	4.3 (1.8–10.3)	32.4 (23.5–44.6)	47.4 (35.2–63.8)
Amlodipine	10.0 (4.8–20.9)	28.1 (18.0–43.7)	45.4 (29.7–69.1)
Lisinopril	8.3 (3.7–18.4)	28.9 18.7–44.4)	47.1 (32.8–67.3)
Aspirin at baseline			
Chlorthalidone	8.8 (6.2–12.5)	29.9 (24.8–36.2)	44.0 (37.4–51.8)
Amlodipine	7.3 (4.5–11.9)	24.1 (18.4–31.6)	41.5 (33.5–51.4)
Lisinopril	10.1 (6.7–15.3)	40.0 (32.4–49.4)	57.4 (47.9–68.7)
No aspirin at baseline			
Chlorthalidone	6.8 (4.9–9.4)	28.0 (23.8–32.9)	48.3 (42.4–54.9)
Amlodipine	8.4 (5.8–12.2)	27.4 (22.1–33.8)	46.7 (39.4–55.4)
Lisinopril	11.9 (8.7–16.4)	32.5 (26.7–39.4)	51.5 (43.8–60.4)
Age 55–64 y			
Chlorthalidone	4.1 (1.8–9.1)	27.1 (19.8–37.1)	38.5 (29.4–50.3)
Amlodipine	1.1 (0.2–7.8)	17.4 (10.5–28.7)	30.4 (20.6–44.8)
Lisinopril	8.3 (4.0–17.3)	23.3 (14.9–36.2)	42.5 (30.1–59.9)
Age 65+ y			
Chlorthalidone	8.6 (6.7–10.9)	29.3 (25.6–33.4)	48.1 (43.2–53.7)
Amlodipine	9.2 (6.8–12.4)	27.7 (23.2–33.0)	47.2 (41.0–54.4)
Lisinopril	11.6 (8.9–15.2)	37.9 (32.6–44.0)	56.2 (49.4–63.8)
Nonsmokers			
Chlorthalidone	7.8 (6.0–10.0)	28.4 (24.8–32.5)	44.9 (40.1–50.2)
Amlodipine	8.5 (6.2–11.7)	27.1 (22.6–32.4)	45.1 (39.0–52.1)
Lisinopril	11.8 (9.0–15.4)	32.6 (27.7–38.4)	51.5 (44.9–58.9)
Smokers			
Chlorthalidone	8.2 (4.9–13.8)	31.2 (23.7–40.9)	54.4 (43.6–67.9)
Amlodipine	4.9 (2.1–11.8)	21.1 (13.6–32.5)	41.8 (30.0–58.1)
Lisinopril	8.1 (4.1–16.1)	49.5 (37.2–65.8)	65.8 (50.9–84.7)

Abbreviations: CI, confidence interval; GI, gastrointestinal.

TABLE IV. The Effect of Antihypertensive Treatment on Risk of Hospitalized GI Bleeding Adjusting for Baseline Characteristics and In-Trial Use of Aspirin and Atenolol

Covariates	Hazard Ratio (95% CI)
Chlorthalidone vs amlodipine	1.06 (0.89–1.26)
Lisinopril vs amlodipine	1.26 (1.04–1.53)
Lisinopril vs chlorthalidone	1.20 (1.01–1.41
Baseline aspirin use (yes/no)	1.07 (0.90–1.27)
Aspirin use ever prior to GI bleed (yes/no)[a]	0.92 (0.78–1.08)
Baseline atenolol use (yes/no)	1.04 (0.69–1.55)
Atenolol use ever prior to GI bleed (yes/no)[a]	0.69 (0.57–0.83)
Age (per year)	1.05 (1.04–1.06)
Black (yes/no)	1.03 (0.97–1.32)
Male (yes/no)	1.27 (1.04–1.48)
Hispanic (yes/no)	0.99 (0.78–1.25)
Smoker (yes/no)	1.35 (1.12–1.61)

Abbreviations: CI, confidence interval; GI, gastrointestinal.

[a]Time-dependent covariate.

Data examining the association between CCB therapy and GI hemorrhage are sparse. Two randomized clinical trials have reported a significant association between CCBs and increased hemorrhage. However, these trials did not examine GI hemorrhage, and instead reported non–stroke-related bleeding[9] and major surgical bleeding[11] and were terminated prematurely[9,11] or had a small number of endpoints.[11] In contrast to the clinical trials suggesting an association between CCB therapy and hemorrhage, ALLHAT has a longer follow-up, a much larger sample size, and a larger number of hospitalized GI bleeding outcomes.

The relationship between CCB therapy and GI bleeding in the cohort, case-control studies, and previously reported clinical trials is inconsistent. Our results are in agreement with the majority of published data that do not support an association between CCB therapy and GI hemorrhage. The cumulative evidence includes multiple case-control studies,[31,35] a large retrospective cohort study involving more than 100,000 patients,[36] and a surgical study that did not demonstrate an association between perioperative CCB therapy and major bleeding (HR, 0.92; 95% CI, 0.65–1.28).[37] In addition, there are several lines of evidence that suggest that the association between GI bleeding and CCBs described in previous studies may be explained by factors that are not causal.

First, the Pahor[12] and Kaplan[13] studies compared CCB-treated patients to a reference group on β-adrenergic antagonist therapy. β-Adrenergic antagonists are known to prevent bleeding from gastric and esophageal varices.[38] In addition, because variceal bleeding has been estimated to be responsible for up to 30% of all upper GI tract bleeding,[39] it is possible that increased associations of bleeding observed relative to a β-adrenergic antagonist reference group[12,14] reflect a therapeutic benefit of β-blockers rather than a prohemorrhagic effect of CCBs.

Our analysis of data from ALLHAT suggests that the use of atenolol was associated with a lower rate of GI bleeding, although, in this trial, assignment to atenolol was not random and thus no definitive conclusion can be drawn. However, our finding is consistent with the previous observation that β-blockers reduce hospitalizations with GI bleeding.[38]

Second, it is possible that exposure misclassification could result in a spurious association between CCBs and bleeding. For example, Pahor and colleagues[12] comment that both "exposure and outcome may have been misclassified" in their study because medications were verified only at the inception of the study and 3 years afterward. This concern is supported by the observation that in their analysis,[12] the association between NSAID use and bleeding was much lower than that reported by other investigators.[32,33]

Third, because a trend of decreasing association between GI bleeding and CCBs after adjustment for potential confounders was observed in multiple studies,[13–15,31,35] the association between CCB therapy and GI bleeding may have also represented an observation that participants taking CCBs were significantly more ill than the reference populations with which they were compared, as has been previously suggested in several observational studies.[14,15,31,33] In addition, among studies that describe an association between CCBs and bleeding, no specific agent has been consistently associated with bleeding.[11–16]

The 5-year rates of hospitalized GI bleeding in ALLHAT were 44.4 events, 46.6 events, and 54.0 events per 1000 participants for amlodipine, chlorthalidone, and lisinopril (9.1, 9.5, and 11.0 events per 1000 person-years, respectively) (data not shown). These values are slightly higher relative to an ancillary study of hypertensive patients older than 65 years enrolled in the Cardiovascular Health Study (CHS) (9.9 and 6.0 events per 1000 person-years in individuals using CCBs or other antihypertensive agents, respectively).[13] The total incidence of GI bleeding across the CHS cohort was 6.8 events per 1000 person-years.[30] Several differences between ALLHAT and CHS may account for the different rates of GI bleeding between the 2 studies. First, the CHS cohort was likely to be healthier than ALLHAT participants at baseline. Second, ALLHAT obtained data from Medicare and VA databases. In contrast, CHS did not include VA patients, leaving the possibility that difference between the 2 study populations may exist. Third, although both studies reviewed hospital discharge records for selected *ICD-9* codes related to GI bleeding, ALLHAT used a different number of *ICD-9* codes and as such could have had a broader definition of GI bleeding (CHS used *ICD-9* codes 531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 533.6; 534.0, 534.2, 534.4, 534.6, 569.0, 578.0, 578.1, and 578.9, respectively).[40] ALLHAT did not include code 569.0, but included the other codes used by CHS, as well as 459.0, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, and 535.61. The *ICD-9* coding of GI bleeding employed by Pahor and colleagues[12] was more restrictive than that used by ALLHAT but cannot explain the differences in results with respect to hospitalized GI bleeding.[29]

Finally, the reasons behind the increased risk of bleeding among diabetic participants are not clear and are likely multifactorial but cannot solely be attributed to aspirin use.[41] In a recent paper, De Berardis and colleagues,[42] looking at a population-based cohort in Italy, used administrative data to determine that patients with diabetes had a high rate of bleeding, although it was not independently associated with aspirin use. In patients with acute coronary syndrome, GI hemorrhage is associated with diabetes as well as hypertension.[43] Further, diabetic patients with peptic ulcer bleeding have poorer outcomes, including greater mortality, than nondiabetic patients.[44] Diabetic angiopathy, impaired healing, autonomic neuropathy, and increased susceptibility to infection may be at least partially responsible for the poor outcomes and may contribute to the cause of the bleeding itself.[41,44]

Surprisingly, our analysis found that participants randomized to a lisinopril-based regimen had the highest frequency of hospitalized GI bleeding events of the 3 randomized groups. Angiotensin-converting enzyme (ACE) inhibitor therapy has been associated with decreased fibrinogen and von Willebrand factor levels in patients with heart failure,[45] and has been associated with decreased levels of plasminogen-activating inhibitor-1 (PAI-1)[40,46] and fibrinogen,[47] compared with patients treated with amlodipine. Amlodipine, in contrast, while not being associated with decreases in PAI-1 or fibrinogen, has been associated with an increase in tissue plasminogen activator levels.[40] The clinical significance of these measurements as related to the frequency of GI bleeding is not certain, and our review did not identify other clinical trials or case reports suggesting a relationship between ACE inhibition and increased GI bleeding.

STUDY LIMITATIONS

The present study does have limitations. Because amlodipine was the only CCB studied in ALLHAT, the results are limited in addressing the safety of other CCBs. However, our primary goal is not to prove the safety of other CCBs, but, in reporting the ALLHAT findings, to add to the large pool of existing data regarding CCB therapy and GI hemorrhage. Second, our analysis of VA and CMS data identified participants who were hospitalized with a GI hemorrhage, although we cannot determine whether the bleeding was a cause or consequence of hospitalization. However, any error related to this would be observed across the entire study and would not be expected to be the basis of a differential comparison in the 3 study arms included in this report. Finally, information on aspirin usage was collected only biannually and by patient report. Information on the use of NSAIDs or anticoagulation therapy was not collected.

CONCLUSION

In ALLHAT, amlodipine therapy did not increase the risk of hospitalized GI hemorrhage when compared with the participants treated with a diuretic. Furthermore, in a post-hoc comparison, participants treated with amlodipine had significantly fewer occurrences of hospitalized GI bleeding than participants randomized to a lisinopril-based regimen. The apparent increase in hospitalizations with GI bleeding in those treated with lisinopril has not been observed previously in trials of ACE inhibitors. The relationship between ACE inhibitor therapy and hospitalized GI hemorrhage may warrant further investigation in other studies.

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